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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/623,205	07/18/2003	Maria Palasis	104914-160	2843

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EXAMINER
AFREMOVA, VERA

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 09/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/623,205	PALASIS, MARIA	
	Examiner	Art Unit	
	Vera Afremova	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35 and 37-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-35 and 37-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/22/2006 has been entered.

Claims 1-35 and 37-45 as amended on 4/27/2006 are under examination.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 1, 5, 6, 10-14, 17, 18, 20, 22, 23, 27-31, 35, 37, 38, 42-44 and 45 as amended remain rejected under 35 U.S.C. 102(b) as being anticipated by Kocher et al. ("Neovascularization of ischemic myocardium by human bone-marrow-derived angioblasts prevents cardiomycete apoptosis, reduces remodeling and improves cardiac function". Nature Medicine. April 2001. Vol. 7, No. 4, pages 430-436) as explained in the prior office action and for the reasons below.

Claims as amended are directed to a method of producing "a graft of muscle tissue" in damaged or diseased tissue of a subject in need thereof, comprising steps of (a) isolating stem cells from peripheral blood of a donor by apheresis; and (b) implanting a population of the isolated stem cells into the damaged or diseased tissue, whereby implantation produces "a graft of muscle tissue" in the damaged or diseased tissue.

Some claims are/are further drawn to the damaged or diseased tissue(s) including tissue striated muscle, ischemic tissue, necrotic tissue, myocardium, skeletal muscle and/or heart. Some claims are further drawn to administration of a mobilization factor to the donor to mobilize the stem cells into peripheral blood, the mobilization factors including GM-SF. Some claims are further drawn to fractionating the stem cells prior implantation including FACS and density gradient centrifugation. Some claims are further drawn to implantation of cells at the site of disease or damage.

The reference by Kocher et al. discloses a method of treating damaged or diseased tissue such as infracted myocardium wherein the method comprising steps of (a) isolating G-CSF mobilized CD34+ stem cells from peripheral blood of a human donor by apheresis (for example: see page 430, col. 2, last par.; page 435, col. 1, last par.); and (b) implanting a population of the isolated stem cells into the damaged tissue of rats by injection (fig. 2 or fig. 3), wherein the method results in the neoangiogenesis and in the implantation of the stem cells within the myocardial tissues (Fig. 2, e), thus, producing "a graft of muscle tissue" in the damaged myocardium. The reference by Kocher et al. discloses that the stem cells were collected and fractioned including leukopheresis, magnetic beads coated with antibodies and FACScan analysis and, thus, fractioned by density centrifugation and fractioned by FACS within the

meaning of the claims. In particular, Kocher et al. disclose that intravenous injection of freshly obtained human CD34+ cells resulted in infiltration of these stem cells into infarct zone of LAD-ligated rats (page 432, col. 2, par. 2, lines 1-4) and that further examination revealed significant increase in infarct zone microvascularity, cellulary density, etc. and improved myocardial function (page 432, col. 2, par. 2, lines 1-4; Fig. 3). Thus, a population of the isolated stem cells have been implanted into tissue in need of treatment or at the site of damage including striated muscle, ischemic tissue, necrotic tissue, myocardium and/or heart within the meaning of the claims.

The claimed term "a graft of muscle tissue" is a generic term as claimed and as disclosed. No histological analysis of "graft of muscle tissue" with the "implanted" stem cells is demonstrated by the applicant (specification pages 24-26). Thus, given a broadest reasonable interpretation, a generic "graft of muscle tissue" comprises a vascular structure. The revascularization protects myocytes and/or muscle cells against apoptosis and provides for improved function of muscle tissue as a whole. The reference by Kocher et al. clearly teaches that the stem cells isolated from peripheral blood were implanted into damaged myocardium, thereby preventing cardiomycete apoptosis and improving cardiac function.

Therefore, the cited reference anticipates the claimed invention.

2. Claims 1, 9-14, 17, 18, 21, 26-31 and 41-45 as amended remain rejected under 35 U.S.C. 102(b) as being anticipated by Kalka et al. ("Transplantation of *ex vivo* expanded endothelial progenitor cells for therapeutic neovascularization". PNAS. March 28, 2000. Vol. 97, No. 7, pages 3422-3427) as explained in the prior office action and for the reasons below.

Claims are directed to a method of producing "a graft of muscle tissue" in damaged or diseased tissue of a subject in need thereof, comprising steps of (a) isolating stem cells from peripheral blood of a donor by apheresis; and (b) implanting a population of the isolated stem cells into the tissue, whereby implantation produces "a graft of muscle tissue" in the damaged or diseased tissue.

Some claims are/are further drawn to the damaged or diseased tissue(s) including tissue striated muscle, ischemic tissue, necrotic tissue and/or skeletal muscle. Some claims are further drawn to fractionating the stem cells prior implantation including FACS and density gradient centrifugation. Some claims are further drawn to additional step of ex vivo expanding the cells prior to the implanting step. Some claims are further drawn to implantation of cells at the site of disease or damage.

The reference by Kalka et al. discloses a method of treating a damaged or diseased muscle tissue of a subject in need thereof, the method comprising steps of (a) isolating stem cells from peripheral blood of a donor (for example: page 3422, col. 2, section Materials and Methods, lines 1-2); and (b) implanting a population of the isolated stem cells into the damaged muscle tissue of murine hindlimb ischemia model (for example: page 3422, abstract, lines 7-9; page 3423, col. 1, last par.), wherein the method results in the neovascularization of the damaged muscle tissue and in the implantation of the donor stem cells within the damaged skeletal muscle for example: page 3422, abstract, lines 9-11; page 3425, col.2, par. 3, lines 1-4; Fig. 5), thereby, producing "a graft of muscle tissue" that provides for the improved function of the damaged or diseased tissue within the meaning of the claims. The reference by Kalka et al. discloses that the stem cells were fractionated prior implantation including FACS and density gradient

centrifugation (page 3422, col. 2, par. 2 and last par.) and the stem cell were ex vivo expanded prior implantation step (title; page 3422, col. 2, par. 2). In particular, the reference by Kalka et al. teaches that transplantation of human peripheral blood derived stem cells or endothelial progenitors into mice with hind limb ischemia resulted in recovery of blood flow, improved capillary density and neovascularization of the damaged skeletal muscle. The animal marine model with hindlimb ischemia received intracardiac injection of human *ex vivo* expanded and labeled epithelial progenitors derived from peripheral blood (page 3423, col. 1, par. 1-2) and the labeled cells were identified in mouse ischemic and necrotic hindlimb tissues (page 3425, col. 2, par. 2, lines 9-13). Thus, a population of stem cells or *ex vivo*-expanded stem cells was implanted into the damaged/diseased muscle tissues or into the site of the damage including striated muscle, ischemic tissue, necrotic tissue and/or skeletal muscle within the meaning of the claims.

The claimed term "a graft of muscle tissue" is a generic term as claimed and as disclosed. No histological analysis of "graft of muscle tissue" with the "implanted" stem cells is demonstrated by the applicant (specification pages 24-26). Thus, given a broadest reasonable interpretation, a generic "graft of muscle tissue" comprises a vascular structure. The revascularization protects muscle cells against apoptosis and provides for improved function of muscle tissue as a whole. The cited reference by Kalka et al. teaches that transplantation of human peripheral blood derived stem cells or endothelial progenitors resulted in improved recovery and capillary density in the skeletal muscle tissue of the ischemic hindlimbs (page 3425, last par.), thereby, providing for the tissue salvage (page 3426, col. 1).

Therefore, the cited reference anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 1-35 and 36-45 as amended are rejected under 35 U.S.C. 103(a) as being unpatentable over Kocher et al. ("Neovascularization of ischemic myocardium by human bone-marrow-derived angioblasts prevents cardiomycete apoptosis, reduces remodeling and improves cardiac function". Nature Medicine. April 2001. Vol. 7, No. 4, pages 430-436) and Kalka et al. ("Transplantation of *ex vivo* expanded endothelial progenitor cells for therapeutic neovascularization". PNAS. March 28, 2000. Vol. 97, No. 7, pages 3422-3427) taken with US 5,199,942 (Gillis) (IDS reference).

Claims are directed to a method of producing a graft of muscle tissue in damaged or diseased tissue of a subject in need thereof, comprising steps of (a) isolating stem cells from peripheral blood of a donor by apheresis; and (b) implanting a population of the isolated stem cells into the tissue, whereby implantation produces a graft of muscle tissue in the damaged or diseased tissue. Some claims are/are further drawn to the damaged or diseased tissue(s) including tissue striated muscle, ischemic tissue, necrotic tissue, myocardium, skeletal muscle, heart and/or liver. Some claims are further drawn to administration of a mobilization factor to the donor to mobilize the stem cells into peripheral blood, the mobilization factors including GM-SF. Some claims are further drawn to administration of engraftment factor to promote engraftment of the stem cells in the subject. Some claims are further drawn to fractionating the stem cells prior

implantation including FACS and density gradient centrifugation. Some claims are further drawn to additional step of ex vivo expanding the cells prior to the implanting step. Some claims are further drawn to implanting the cells at the site of disease or damage. Some claims are further drawn to the subject of implantation including same as donor, HLA-matched to the donor, human.

The references by Kocher et al. and Kalka et al. are relied upon as explained above for the disclosure of a method of treating damaged or diseased tissue and/or of producing an improved and functional graft of muscle tissue in the damaged or diseased tissue of a subject in need thereof by implanting peripheral blood derived stem cells. The cited references teach that transplantation of the donor peripheral blood derived stem cells results in neovascularization and amelioration of the damaged muscle tissues such as striated muscle, ischemic tissue, necrotic tissue, myocardium, skeletal muscle, heart. Both cited references demonstrate that the donor peripheral blood derived stem cells were incorporated or implanted into recipient damaged tissues, thus, producing an improved and functional graft of muscle tissue in the recipient. Both cited references recognize presence of stem cells in circulating blood or peripheral blood. The reference Kocher et al. also teaches mobilization of stem cells from bone marrow into peripheral blood by administration of mobilization factors to the stem cell donor. The reference Kalka et al. also teaches that *ex vivo* culture strategy allows expansion and considerable increase in the original number of harvested cells (page 3426, col. 2, par. 2). Both cited references suggest that transplantation of stem and/or progenitor cell population has potential to significantly improve damaged or diseased tissue in patients, and, thus, humans. Both cited references suggest transplantation of stem cells alone in combination with currently used therapies or with

cytokines. For example: see Kocher et al. at abstract and see Kalka et al. at last lines of the articles on page 3427.

Thus, although the cited references recognize and suggest combined therapies or transplantation of stem cells with additional drugs, they are lacking particular disclosure about some additional particular drugs or cell engraftment factors. However, US 5,199,942 (Gillis) teaches administering engraftment factors including GM-CSF, IL-3, SCF and others following transplantation of hematopoietic cells in the method for improving cell transplantation (col. 3, lines 39-45). US 5,199,942 also teaches administering recruitment or mobilization factors including GM-CSF, IL-3, SCF and others prior to cell collection (col. 3, lines 30-36) and ex vivo expansion of progenitor cells (col. 3, lines 46-52) in the method for improving cell transplantation.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to administer engraftment factors in combination with stem and/or progenitor cell transplantation with a reasonable expectation of success for improving cell transplantation as suggested by Kocher et al. and Kalka et al. and as taught by US 5,199,942 (Gillis). One of skill in the art would have been motivated to *ex vivo* expand the stem or progenitor cells prior transplantation for the expected benefits in expanding or increasing number of harvested cells as taught by Kalka et al. and taught by US 5,199,942 (Gillis). One of skill in the art would have been motivated to use cell derived from a donor that is HLA-matched to the host for the expected benefits in minimizing immune response and avoiding transplant rejection.

Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary. The claimed subject matter fails to patentably distinguish

over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

2. Claims 1-35 and 37-45 as amended are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,387,369 (Pittenger et al) and US 6,261,549 (Fernandez et al) taken with Orlic et al. (IDS reference; Nature. 2001, Vol. 410, pages 701-705) and Orlic et al. ("Cytokine-mobilized stem cells traffic to infracted hearts and regenerate functional myocardium resulting in improved survival". Blood. 2001. Vol. 98, No. 11, part 1, page 810a.).

Claims as above.

US 6,387,369 teaches a method for regeneration of repair of striated cardiac muscle or for producing "a graft of muscle tissue" by implanting mesenchymal stem cells (MSCs) in the damaged tissue, for example: see entire document including col. 1, lines 41-50. The source for the isolation of the MSCs in the method of administration is a generic "MSC-containing tissue" as disclosed by US 6,387,369, for example: col. 1, line 61. However, US 6,261,549 teaches that the MSCs intended for administration and muscle tissue repair are collected from the peripheral blood of the donors treated the growth factors G-CSF and/or GM-CSF, for example: see entire document including abstract. The cited patents US 6,387,369 and US 6,261,549 also encompass cell sorting and ex-vivo expansion of the cells prior to administration.

Further, the cited references by Orlic et al. teach and demonstrate that bone marrow-derived stem cells mobilized by cytokines into peripheral blood regenerate infarcted myocardium.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to implant the stem cells isolated from peripheral blood into the damaged striated muscle tissue with a reasonable expectation of success in producing a graft of muscle tissue because the prior art teaches and/or suggests the use of stem cells mobilized by cytokines into peripheral blood for regeneration of striated cardiac muscle as adequately demonstrated by the cited references. Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Response to Arguments

Applicant's arguments filed 4/27/2006 have been fully considered but they are not persuasive.

With regard to the claim rejections under 35 U.S.C. 102(b) as being anticipated by Kocher et al. Applicant appears to argue that the prior art stem cells are hematopoietic cells as evidenced by marker CD34+ and, thus, these cells would not be used for implantations as intended to treat damaged muscle tissues. However, the pending claims are not limited to the specific markers of the stem cells. Moreover, the scope of the instant invention encompasses the use of any and all stem cells including mesenchymal stem cells, hematopoietic stem cells and some unidentified "side" population cells (page 10, lines 1-4) and the applicants' particular disclosure appear to describe isolation and implantation of hematopoietic CD34+ cells (page 24).

Thus, the cited prior art teaches the use of the same population of "stem cells" as claimed and when read in the light of specification.

With regard to the claim rejections under 35 U.S.C. 102(b) as being anticipated by Kocher et al. or by Kalka et al. Applicant argues that the methods of cited references result in neovascularization rather than producing "a graft of muscle tissue" as required by amended claims (response page 9). This argument is not found particularly persuasive because the claimed term "a graft of muscle tissue" is a generic term as claimed and as disclosed and because the histological analysis of "graft of muscle tissue" with the "implanted" stem cells is not demonstrated by the applicant (specification pages 24-26). Thus, given a broadest reasonable interpretation, a generic "graft of muscle tissue" comprises some vascular structure. The revascularization protects muscle tissue cells against apoptosis and provides for improved function of a muscle tissue as a whole. Both cited references Kocher et al. and/or Kalka et al. demonstrate with an aid of fluorescent labels that the donor peripheral blood derived stem cells were incorporated or implanted into recipient damaged tissues including skeletal and myocardial muscles, thus, producing "a graft of muscle tissue" in the recipient damaged or diseased muscle tissues within the broadest meaning of the pending claims.

Claims rejection under 35 U.S.C. 103 over the teaching by Lagasse et al. ("Purified hematopoietic stem cells can differentiate into hepatocytes in vivo". Nature Medicine. November 2000, Vol. 6, No. 1, pages 1229-1234) has been withdrawn due to cancellation of claims drawn to a liver as damaged tissue and/or organ.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (571) 272-0914. The examiner can normally be reached from Monday to Friday from 9.30 am to 6.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached at (571) 272-0926. The fax phone number for the TC 1600 where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology center 1600, telephone number is (571) 272-1600.

Vera Afremova,

AU 1651

September 1, 2006

V. Afremova

VERA AFREMOVA

PRIMARY EXAMINER